The Shocking Lack of Evidence for Implantable Cardioverter Defibrillators for Heart Failure; with or without Cardiac Resynchronisation.

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Clinical research has transformed the lives and expectations of many patients with heart failure, especially for patients aged <75 years with symptomatic, clinically stable, chronic heart failure and a reduced left ventricular ejection fraction (1, 2). The median survival for such patients with moderate or severe symptoms in the 1980's was less than 5 years. Life expectancy has more than doubled for those who now receive contemporary specialist care. This change in prognosis has been brought about both by slowing or reversing ventricular dysfunction and congestion and by reducing the risk of sudden (presumed arrhythmic) death (1, 3). Many patients are keen to hear this more optimistic view rather than the previous doom-laden message so common in the heart failure literature (1). However, greater longevity leads to more frailty and senescence, which are becoming increasingly important limitations to the benefits of treatments for heart failure and new therapeutic targets (4). Clinical trialists need to be aware of this evolution in the natural history of heart failure when designing future research.

One of the great advances in care for heart failure are cardiac resynchronisation therapy pacemakers (CRT-P) that may also have an implantable cardioverter defibrillator (ICD) function (CRT-D). Improvement in battery-life, which may now exceed 10 years, means that these devices now often out-live their hosts. CRT was designed to optimise the sequence of atrial and bi-ventricular contraction, thereby reducing functional mitral regurgitation, improving left ventricular performance, preventing ventricular tachy- and brady-arrhythmias, improving well-being and prolonging life (5). Selection for CRT is relatively straightforward and should be considered for many patients with heart failure, a reduced left ventricular ejection fraction (HFrEF) in sinus rhythm and a QRS duration >130ms (6). Although guidelines also recommend CRT for patients with atrial fibrillation, this seems somewhat premature (7). For patients with atrial fibrillation and HFrEF, no randomised controlled trial has specifically investigated the benefits of pulmonary vein ablation and CRT over and above guideline-recommended pharmacological management, although this might have accounted for some of the benefit observed in trials such as CASTLE-AF (7). Only one small randomised trial (n = 102) has investigated bi-ventricular pacing with atrio-ventricular node ablation

compared to avoiding pacing altogether (7). Several trials do show that bi-ventricular is superior to right ventricular pacing in patients with atrial fibrillation and HFrEF, but this may reflect the deleterious effects of right ventricular pacing rather than any benefit of bi-ventricular pacing without the ability to deliver atrio-ventricular resynchronisation (7).

The ICD was designed to terminate malignant ventricular tachyarrhythmias, either by delivering a shock or with over-drive pacing and, incidentally, can also prevent lethal bradycardia. There are serious doubts about the utility of ICD in patients with heart failure, especially in older patients, who often have other life-shortening conditions such as diabetes, lung or kidney disease (3, 7-9). Randomised trials suggest that ICDs might only be effective in patients with a LVEF <30% and QRS duration >120ms but with few or no symptoms of heart failure or co-morbid conditions (10, 11). Patients with grossly elevated plasma concentrations of natriuretic peptides are likely to die of progressive heart failure and don't appear to benefit from an ICD (12). Patients with low plasma concentrations of natriuretic peptides may not benefit because they have a good prognosis without device-intervention (13). Basically, ICDs are most effective at preventing sudden arrhythmic death for patients who have some increased risk of arrhythmias but, more importantly, are at low risk of dying for any other reason (Figure). Rather than trying to identify patients at high-risk of sudden death, clinicians should be selecting patients at low-risk of death for any other reason. In clinical practice, only a minority of patients use their ICD during the life-time of the device. The choice is problematic for clinicians and often a difficult discussion with patients.

Advances in pharmacological therapy and CRT have improved ventricular function, which has reduced overall mortality; both sudden death and death due to worsening heart failure. However, it is not clear that the proportion of sudden deaths compared to overall mortality has fallen over the last 20 years and remains about 35% of all deaths and almost 50% of cardiovascular deaths (14). For patients with HFrEF who are unlikely to die of cancer, progressive heart failure or some other problem within the next 10 years, for every 100 ICDs implanted, one or two lives will be

meaningfully prolonged each year and 10-20 lives over a decade. Treatments that prolong life and reduce the risk of dying from progressive heart failure, including CRT, should increase the time alive after ICD implantation and therefore increase the chances of a successful ICD intervention. However, there is a paucity of evidence that CRT-D improves survival compared to CRT-P.

In this issue of the European Heart Journal, Barra et al(15) describe the long-term outcome of 534 people who had received CRT-P and 1,241 who had received CRT-D and had survived the first 5 years after enrolment into a consortium of international patient-cohorts. After adjusting for age and other factors, there was no difference in all-cause mortality or sudden death between those who had received CRT-D rather than CRT-P. Importantly, only 15 patients assigned to CRT-D and 14 to CRT-P died suddenly (adjusted hazard ratio 1.0 [0.45-2.44]). Progression of heart failure and non-cardiovascular disease, which are unlikely to be reduced by an ICD, accounted for two-thirds of deaths.

This was not a randomised trial. The mean age at implantation of CRT-P was 70 years compared to just 64 years for those who received CRT-D, about half of the patients had ischaemic heart disease, >40% had a history of atrial fibrillation and >60% had a QRS duration >150ms. Statistical methodologies may not adequately adjust for observed differences and cannot account for unmeasured confounders. The results might also have been biased by differences in mortality and cause of death prior to the 5-year post-implant baseline. This analysis included only 1,775 of the 5,782 patients initially enrolled. We are not told what happened to the other 4,007 (69%) patients; more than 2,000 had probably died, some will have been lost to follow-up and some may have been followed for less than 5 years. In the largest of the component cohorts, CERTITUDE (n = 1,705)(16), after adjusting for differences in patient-characteristics, more deaths had occurred at two years of follow-up amongst those selected to receive CRT-P rather than CRT-D (adjusted relative risk (aRR) 1.54 [95% confidence interval 1.07-2.21; p=0.02) but there was no substantial increase in sudden death (aRR 1.21, 95% CI 0.45–3.29, P= 0.70). Amongst those who received CRT-P, annual unadjusted

rates for sudden death, death due to heart failure and non-cardiovascular death were, respectively, 1.2%, 7.5% and 3.2% and for CRT-D, respectively, 0.8%, 3.3% and 2.0%.

Current guidelines leave the decision on CRT-D or CRT-P to the treating physician. Not surprisingly there is huge international variation in the preference for CRT-D and CRT-P (17, 18). In view of the difference in cost and complications between CRT-P and CRT-D and the lack of evidence of a difference in efficacy, randomised trials are required to quantify the benefits and risks for each device to help patients and physicians to make the best decisions about treatment. By preventing death from worsening heart failure, CRT may increase the opportunity for an effective ICD intervention. However, CRT might reduce the arrhythmia substrate by improving ventricular function and preventing long-pauses, making the ICD function redundant, especially for people who are at high-risk of dying from problems other than an arrhythmia.

The RESET-CRT [https://clinicaltrials.gov/ct2/show/NCT03494933] has begun to enrol patients in Germany and a similar study is planned in the United Kingdom. Both aim to enrol about 2,000 patients and both have a primary outcome of all-cause mortality. Importantly, the investigators for each trial are in dialogue rather than competition and intend, in due course, to share results.

Legend to Figure

Two-year cause specific mortality and non-fatal vascular events for patients with cardiovascular disease according to New York Heart Association (NYHA) class. Numbers and proportions are a conceptual representation of absolute and relative risk and are not strictly evidence-based. Note that for patients in NYHA Class 4, interventions for sudden arrhythmic death may be ineffective or fail to lead to a meaningful prolongation of life because the patient is likely soon to die of worsening heart failure.

Non-CVD = non cardiovascular death
NFVE = non-fatal vascular event (eg:- myocardial infarction and stroke) – note that events are more likely to be suddenly fatal as heart failure progresses.
SVD = sudden vascular death
RSAD = resuscitatable sudden arrhythmic death
TSAD = terminal (non-resucitatable) sudden arrhythmic death
CRD = congestion-related death, otherwise called death due to worsening heart failure.

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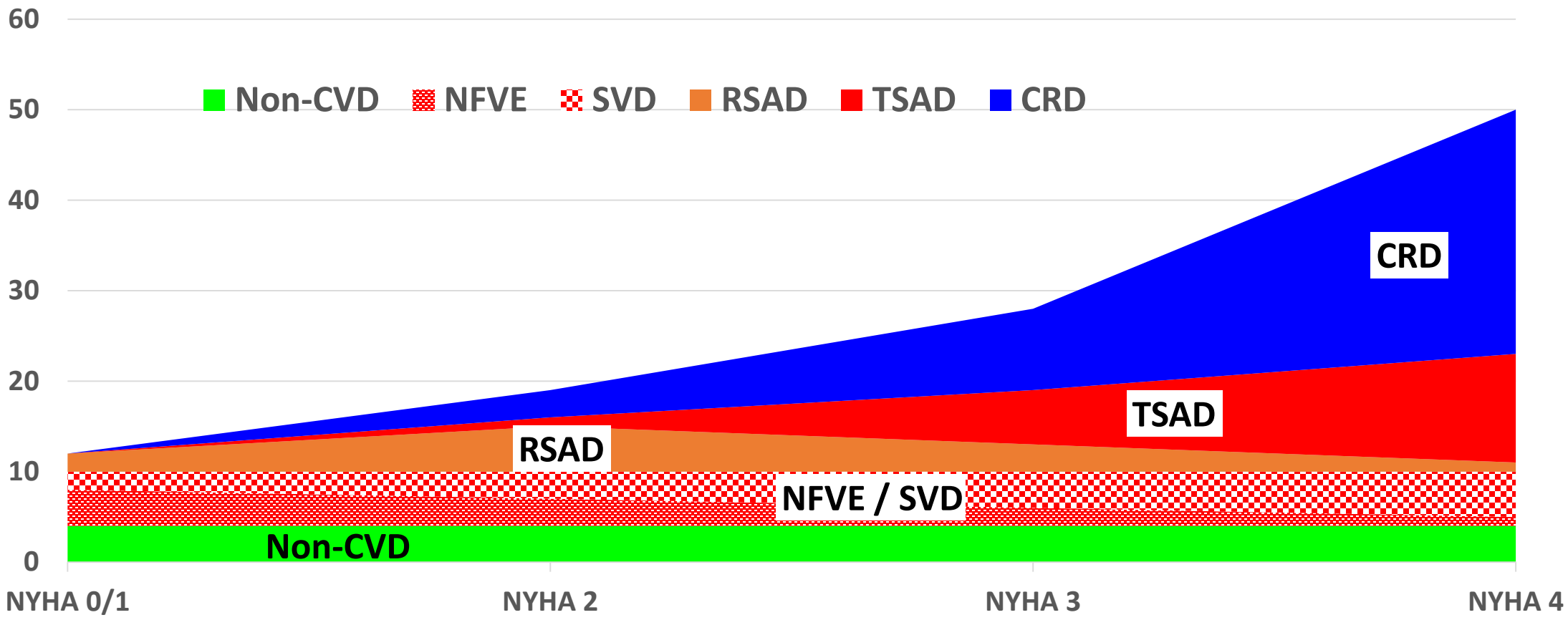

	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths	Absolute Rate	% of Deaths
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	<1%	<1%	1%	5%	6%	21%	12%	24%
RSAD	2%	17%	5%	26%	3%	11%	1%	2%
SVD	2%	17%	3%	16%	4%	14%	5%	10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	21%	4%	14%	4%	8%